PPQ Criteria for Inter- and Intra-batch Variability and Assessment of Homogeneity

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Stage 2 – Process Qualification

- "During the process qualification stage of process validation, the process design is evaluated and determined if it is capable of reproducible commercial manufacture."
  - Design of a facility and qualification of utilities and equipment
  - **Process performance qualification (PPQ).**

Reference: ***Guidance for Industry Process Validation: General Principles and Practices*****. Jan 2011.**

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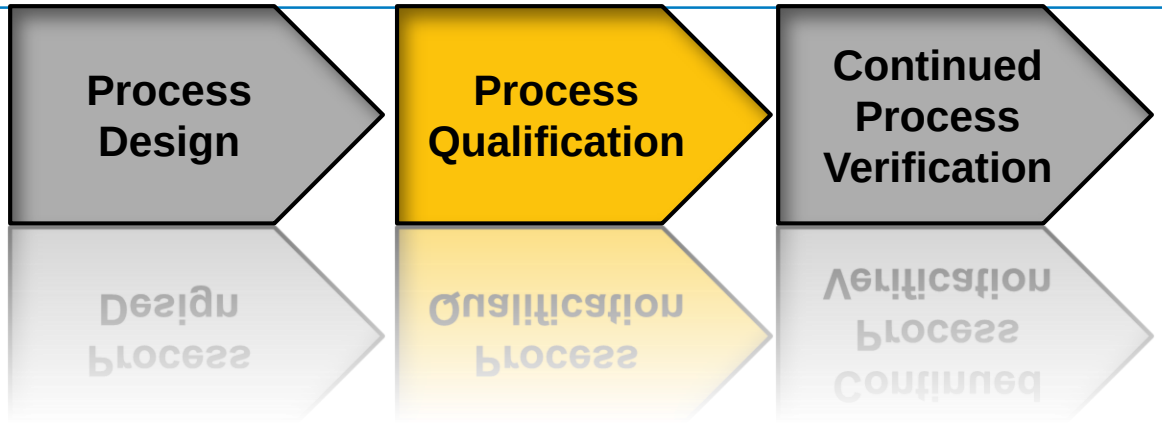
Stage 2 – Process Qualification



- Evaluate the effects of scale
- **Develop PPQ acceptance criteria by characterizing inter-batch and intra-batch variability**
- Design a sampling plan.

Reference: ***Guidance for Industry Process Validation: General Principles and Practices*****. Jan 2011.**

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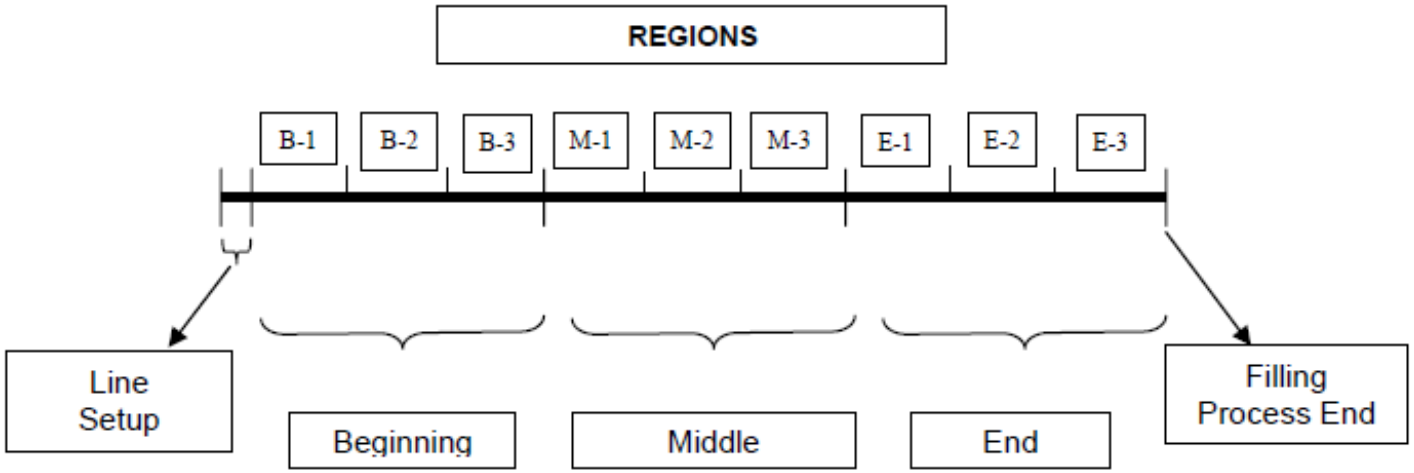
Demonstration of Intra-batch (Within-batch) Variability

- Drug product (DP) homogeneity (uniformity) refers to the sameness of quality attribute(s) across the units that make up a batch.
- Testing performed at release and during stability studies necessitates that homogeneity assessment of DP batches be performed for the justification of release sample size.

Sampling Plan

- For sampling a formulated DP from the hold vessel or during filling of DP into final containers (vials or syringes), one can conceptually divide the filling period into three intervals: Beginning, Middle, and End.
- Samples are selected from each interval to ensure a representative sample of the entire batch.



Equivalence Testing

- To provide the strongest statistical evidence of homogeneity, one can perform a statistical test of equivalence.
- Equivalence tests are performed by computing two-sided 90% confidence intervals for the three mean differences:

$$\mu_{Beginning} - \mu_{Middle}$$

$$\mu_{Beginning} - \mu_{End}$$

$$\mu_{Middle} - \mu_{End}$$

- In order to demonstrate average equivalence, one demonstrates that each difference is less than the equivalence acceptance criterion (*EAC*).

Equivalence Acceptance Criterion

- The *EAC* is based on expected variation in the analytical method.
  - Obtain an estimate of the analytical method standard deviation, σ_M, from analytical qualification or reference standard measurements.
  - All mean differences must be less in absolute value than

$$EAC = 3 \times \sigma_M$$

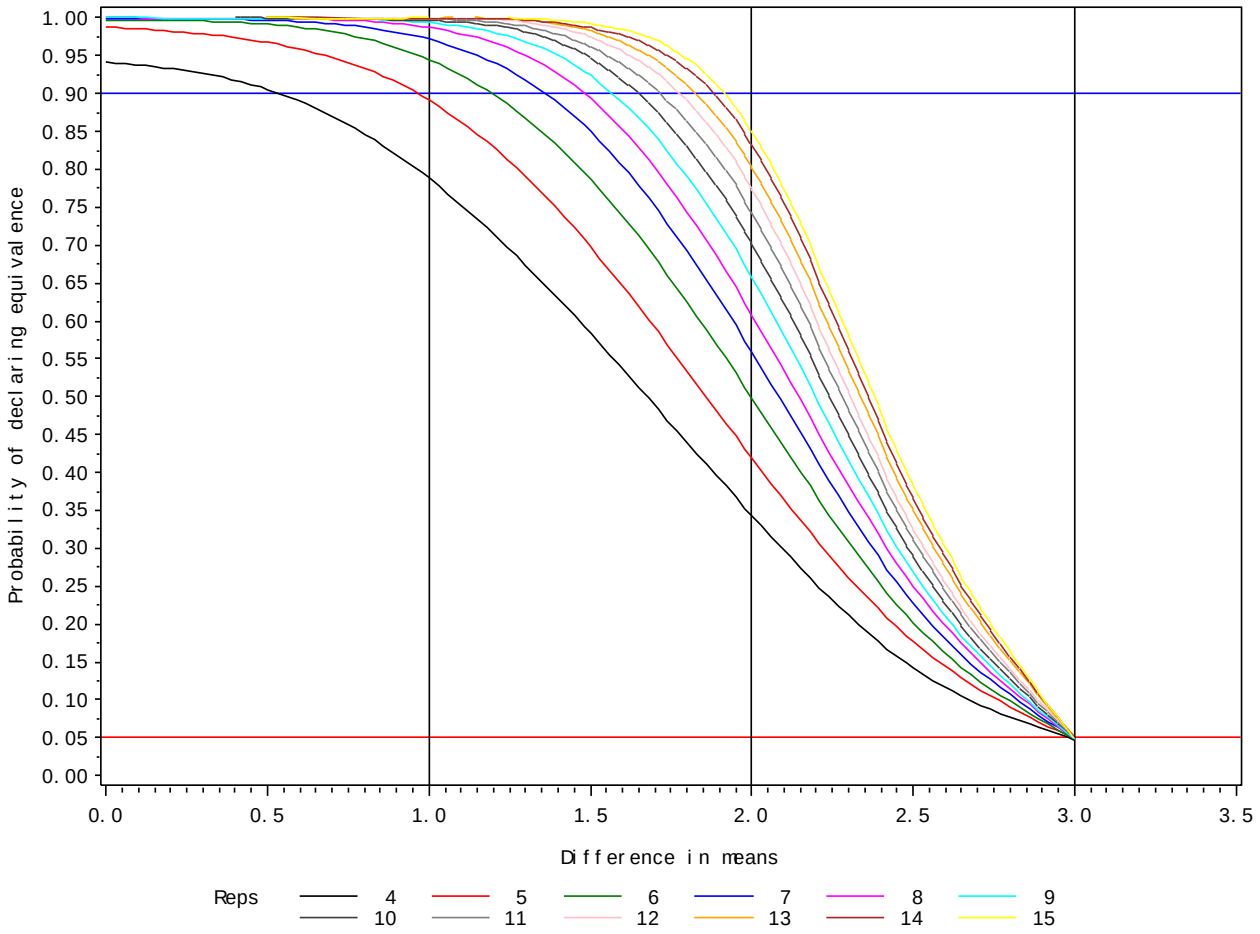
- Note that since all three contrasts must satisfy criterion in order to demonstrate homogeneity, no multiplicity adjustment is needed.
- This is in effect “Six One-Sided Tests” (SOST)

Intersection-Union Tests (IUT)

- A general IUT formulates a null hypothesis that is a union of individual null hypotheses for a set of *k* parameters.
- The alternative hypothesis is an intersection of the individual alternative hypotheses.
- The overall null hypothesis in an IUT can be rejected only if each of the *k* individual null hypotheses can be rejected.
- Berger (1982) proved that if each of the individual tests is performed at test size no greater than α, the overall test has test size no greater than α. (IUTs can be conservative).
- Under certain conditions, he also showed that if one of the tests has test size equal to α, then the overall test has test size equal to α.
- The TOST is a simple case of an IUT, but other IUT tests have greater power than TOST (Berger and Hsu 1996).

Sample Size

- Sample size at each position can be obtained by power calculation.



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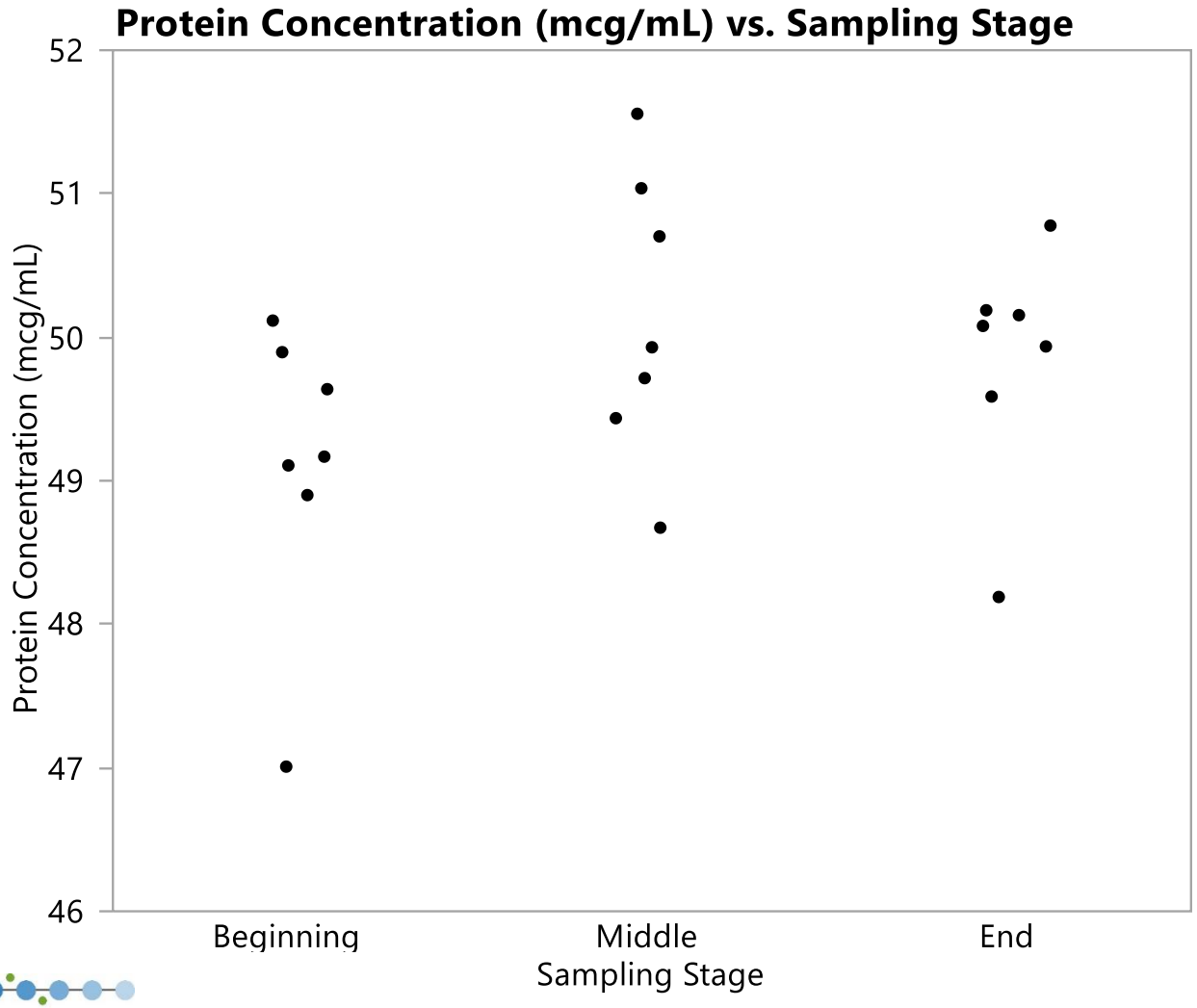
Example


Protein Concentration (mcg/mL) vs. Sampling Stage
52
51
50
49
48
47
46
Protein Concentration (mcg/mL)
Beginning
Middle
End
Sampling Stage

Example

- The analytical method has a reported %RSD of 2 at a target protein concentration of 50 mcg/mL
- Thus, the standard deviation at the target concentration is

$$50 \times 0.02 = 1 \text{ mcg/mL}.$$

- An appropriate *EAC* for this demonstration is thus

$$3 \times 1 = 3 \text{ mcg/mL}$$

Source of variation	Degrees of freedom	Mean square
Region	$n_1 = a - 1 = 2$	$S_1^2 = 1.96$
Error with regions	$n_2 = a(r-1) = 18$	$S_2^2 = 0.907$

a=3 regions, r=7 samples per region

Example

The 90% two-sided confidence interval on the difference $\mu_B - \mu_M$ is

$$L = \bar{Y}_B - \bar{Y}_M - t_{0.95:a(r-1)}\sqrt{S_2^2\left(\frac{1}{r}+\frac{1}{r}\right)}$$

$$= 49.12 - 50.15 - 1.73\sqrt{0.907\left(\frac{1}{7}+\frac{1}{7}\right)} = -1.91 \text{ mcg/mL}$$

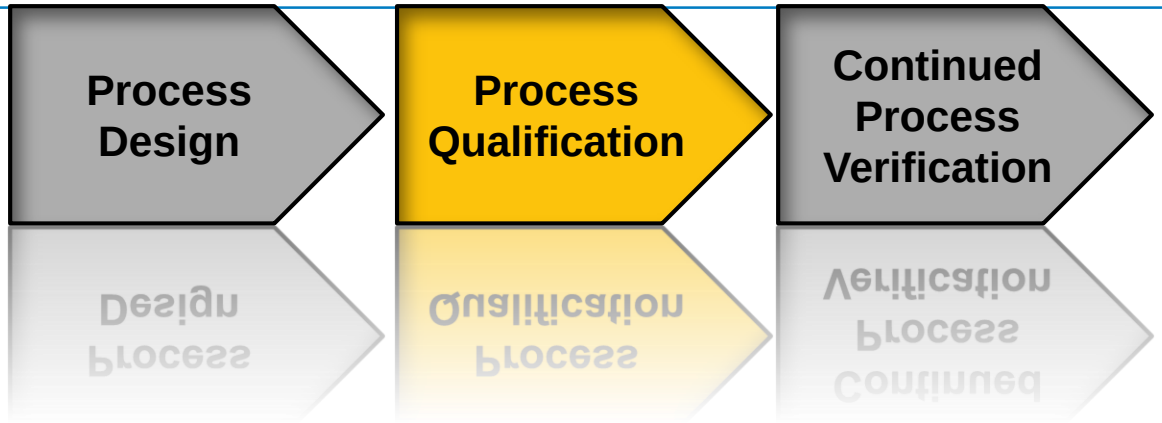
$$U = \bar{Y}_B - \bar{Y}_M + t_{0.95:a(r-1)}\sqrt{S_2^2\left(\frac{1}{r}+\frac{1}{r}\right)} = -0.15 \text{ mcg/mL}$$

The computed 90% two-sided intervals for $\mu_B - \mu_E$ and $\mu_M - \mu_E$ are

(-1.60, 0.16) and (-0.57, 1.19), respectively.

All intervals between -3 and +3 and homogeneity has been validated

Stage 2 – Process Qualification



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Demonstration of Inter-batch Variability

- Process characterization data collected in Step 1, Process Design can be used to derive criteria for critical quality attributes (CQA) when the process is operated at targeted critical process parameters (CPP) values.
- These criteria define expected ranges for the CQA when the process is operating as intended.
- Successful PPQ requires demonstration that these criteria can be met on a consistent basis.

The Starting Point: Small-Scale Models

- Small-scale models can be developed and used to support process development studies by
  - Identifying the process parameters that have an effect on product CQAs.
  - Determination of the functional relationships that link process parameters to product CQAs.
- The development of a model should account for scale effects and be representative of the proposed commercial process.
- A scientifically justified model can enable a prediction of quality, and can be used to support the extrapolation of operating conditions across multiple scales and equipment.

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Combining Scales

- Pilot-scale data manifests representative sources of variation that are not present in small-scale process characterization studies.
- Opportunities are provided for discovering scale-up effects by combining process learnings from small-scale and pilot-scale studies.
- Combining leverages the causal relationships between critical process parameters (CPPs) and critical quality attributes (CQAs) that are discovered with small-scale data.

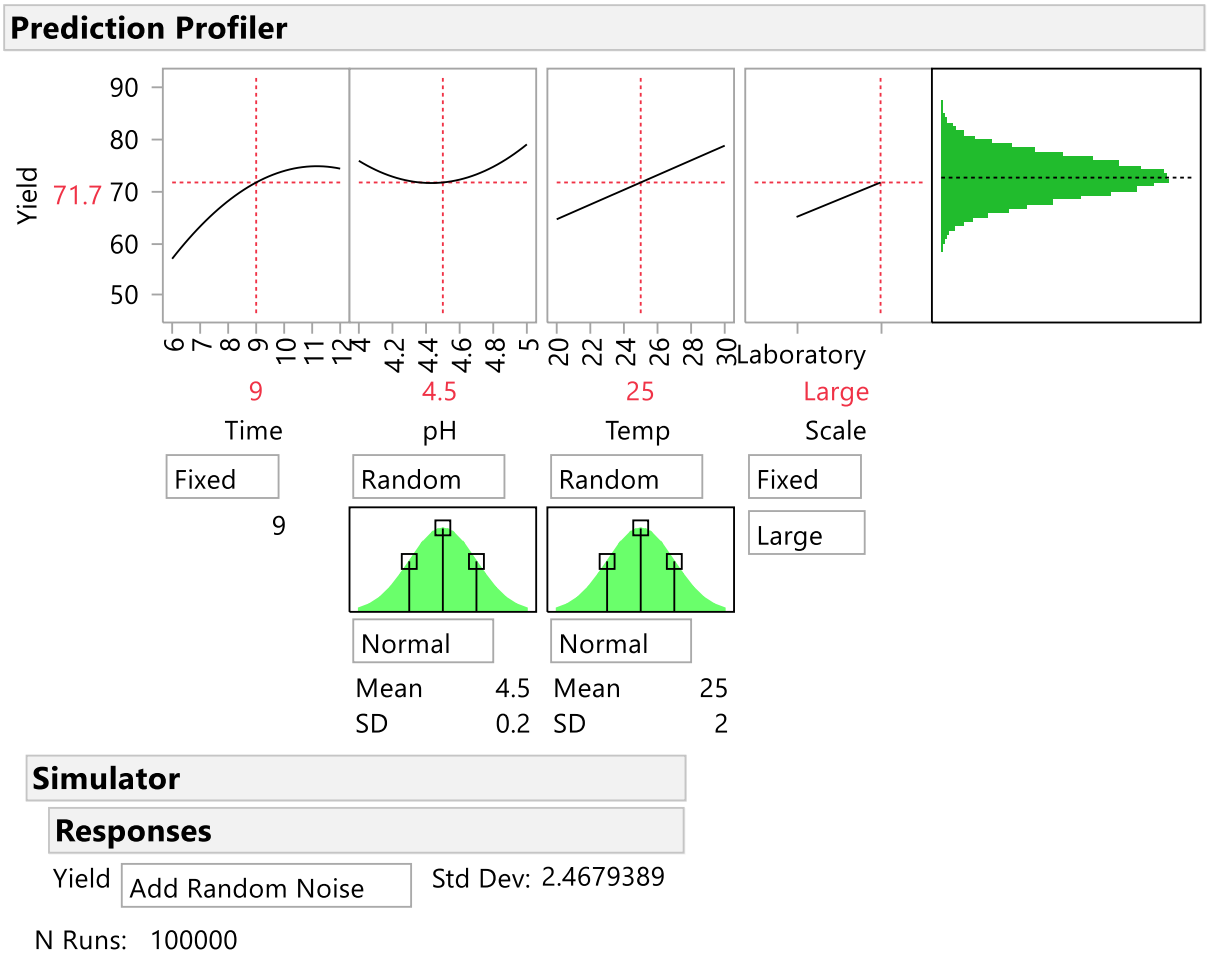
JMP Profiler

- A useful tool for defining PPQ limits is the JMP Profiler.
- Based on combined information from bench studies, pilot studies, and full scale runs, functional relationships are discovered between CQA's and PP's.

JMP Profiler with Simulator

Yield

Term	Estimate	Prob>|t|
Intercept	65.074102	<.0001 *
Time(6,12)	8.6608582	<.0001 *
pH(4,5)	1.5758582	0.0119 *
Temp(20,30)	7.0764138	<.0001 *
Time*Time	-6.002305	0.0004 *
Time*pH	5.0934655	<.0001 *
pH*pH	5.7426946	0.0005 *
pH*Temp	-5.156535	<.0001 *
Scale[Large-Laboratory]	6.6258982	0.0007 *



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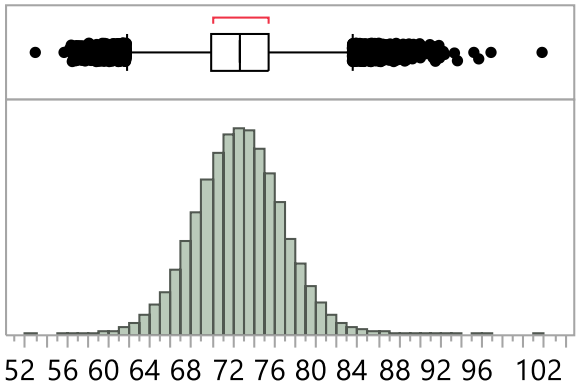

Quantiles		
100.0%	maximum	101.77480844
99.5%		83.943279315
97.5%		80.713511328
90.0%		77.804314439
75.0%	quartile	75.329037619
50.0%	median	72.611665539
25.0%	quartile	69.88714931
10.0%		67.435284994
2.5%		64.549663168
0.5%		61.886363004
0.0%	minimum	52.943224525

Summary Statistics	
Mean	72.621761
Std Dev	4.1161904
Std Err Mean	0.0130165
Upper 95% Mean	72.647273
Lower 95% Mean	72.596249
N	100000

References

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